Delayed Gastric Emptying Occurs Following Acarbose Administration and is a Further Mechanism for its Anti-hyperglycaemic Effect

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The therapeutic effect of acarbose is generally attributed to inhibition of amylase and brush border glucosidases and consequent impaired digestion and absorption of carbohydrates. We have investigated the possibility that acarbose may also influence the rate of gastric emptying by comparing plasma glucose and gastrointestinal hormone responses to an oral sucrose load with and without acarbose in 11 healthy subjects. Gastric emptying was assessed indirectly by measuring circulating paracetamol concentrations following administration of paracetamol along with the sucrose load. Peak plasma glucose, insulin, and glucose-dependent insulinotropic polypeptide (GIP) responses were reduced when sucrose was given with acarbose. There was a significant reduction in post-sucrose paracetamol levels with acarbose suggestive of a significant delay in gastric emptying. The failure of acarbose to induce change in circulating paracetamol concentrations until after 60 min is indicative of a delay in gastric emptying rather than an osmotic malabsorption. The exaggerated and sustained release of glucagon-like peptide-1 (7-36)amide (GLP-1) seen when sucrose was given with acarbose may play a part in the inhibition of gastric emptying. This study indicates that a significant delay in gastric emptying may be an added mechanism contributing to the therapeutic effect of acarbose.

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Introduction

Acarbose is a microbial pseudo-tetrasaccharide which is increasingly used in the treatment of both Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes mellitus. It produces a reduction in glycaemic excursions and insulinaemic responses in the postprandial period,[1,2] and beneficial effects on both carbohydrate and lipid metabolism, with reductions in glycosylated haemoglobin[8] and circulating triglyceride.[1,2] However, most studies have not shown a beneficial effect on body weight, insulin resistance or fasting insulin concentrations.

The therapeutic effects of acarbose are generally attributed to its effects on the digestion and absorption of carbohydrate.[4] Complex dietary polysaccharides are converted by pancreatic amylase and brush border glucosidases to oligo- and monosaccharides prior to transport through the intestinal wall. Acarbose is a potent inhibitor of brush border enzymes such as glucoamylase, dextrinase, maltase, and sucrase.[5,6] In addition, acarbose also inhibits pancreatic amylase and delays digestion of starch.[7]

The delivery of nutrients to the small intestine is a function of the rate of gastric emptying. The generally accepted mechanism of action of acarbose does not suggest an effect on gastric emptying. However, the malabsorption of carbohydrates following acarbose results in stimulation of intestinal motility; mouth to caecum transit times (as indicated by breath hydrogen measurements) have been shown to be reduced by treatment with acarbose.[8] It is not known whether more rapid gastric emptying may be a component of the shorter mouth to caecum transit time.

Accurate measurement of gastric emptying is difficult; standard methods use isotopically-labelled markers. Paracetamol (acetaminophen) has been widely used in the non-invasive assessment of gastric emptying based on the rationale that gastric emptying rate is the major determinant of its circulating concentration.[9–11] The object of the present study was to use this method to determine whether acarbose, when administered with sucrose, has any effect on gastric emptying.

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Subjects, Materials, and Methods

Study Protocol

The study protocol was approved by the Epsom General Hospital Medical Ethics Committee. Written consent was obtained from all participants.

Subjects

Eleven healthy male volunteers (mean ± SD; age: 47.6 ± 7.6 years; BMI: 25.1 ± 0.7 kg m^{-2}), all with normal routine laboratory values (serum electrolytes, liver enzymes, and creatinine), were recruited for study on 2 separate days, a week apart, in random order. All were non-smokers and none was taking medication.

Experimental Procedures

All subjects attended for study on two occasions separated by at least 1 week. Studies were performed after a 12–14 h overnight fast and abstinence from alcohol for 24 h. Studies were carried out with the subjects seated at rest. An indwelling cannula was sited in a forearm vein and kept patent with saline. Subjects were given 100 g of sucrose dissolved in 500 ml of water to which was added 4 g of finely powdered paracetamol (as Pameton™, a combination of paracetamol and methionine); this solution was ingested over 15 min. Venous blood samples were collected through the cannula before (–15 and 0 min) and at 15, 30, 60, 90, 120, 150, 180, and 210 min following sucrose administration. On one of the two visits, subjects were given 100 mg of acarbose (Glucobay™) (two tablets) 3 min before drinking the sucrose/paracetamol solution.

Blood Samples

Blood samples were collected into heparinized tubes containing aprotinin (1000 KIU ml^{-1} blood) for measurement of insulin, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (7-36)amide (GLP-1); into tubes containing fluoride/oxalate for glucose, and into plain glass bottles for paracetamol measurements. Heparinized and fluoride/oxalate samples were centrifuged immediately at 1200 g for 5 min and plasma was separated and frozen at –20 °C in aliquots until analysis. Blood collected into plain glass bottles for paracetamol analysis was centrifuged at 1200 g (for 5 min), 30 min after collection, and serum was separated and stored at –20 °C until analysis.

Laboratory Assays

For each subject, samples from both visits were paired and analysed together. Glucose and paracetamol were measured on an Olympus™ 560 analyser. Glucose was measured by an automated glucose oxidase method. Paracetamol was measured by an enzymatic method with an inter-assay CV of 1.9 % at 30 mg l^{-1} (Quantase™ kit). Insulin, GIP, and GLP-1 were analysed in all heparinized samples by radioimmunoassays that have been described in detail elsewhere.[12–14] The inter-assay CV for GIP at 300 and 497 pmol l^{-1} were 8.6 and 8.9 %, respectively; for insulin at 62.2, 266, and 448 pmol l^{-1} were 25.9, 12.3, and 6.8 %, respectively; for GLP-1 at 22.6 and 64.5 pmol l^{-1} were 17.8 and 15.4 %, respectively.

Statistical Analysis

Total and integrated responses for each analyte were calculated using the trapezoidal rule. Results for the two visits (total and incremental integrated responses and individual time points) were compared using paired Student's *t*-test. Values for $p < 0.05$ were considered significant.

Results

Glucose, insulin, GIP, GLP-1, and paracetamol responses are shown in Figures 1 and 2, and in Table 1. None of the subjects had any adverse gastrointestinal effects during the study.

The plasma glucose peak response was significantly

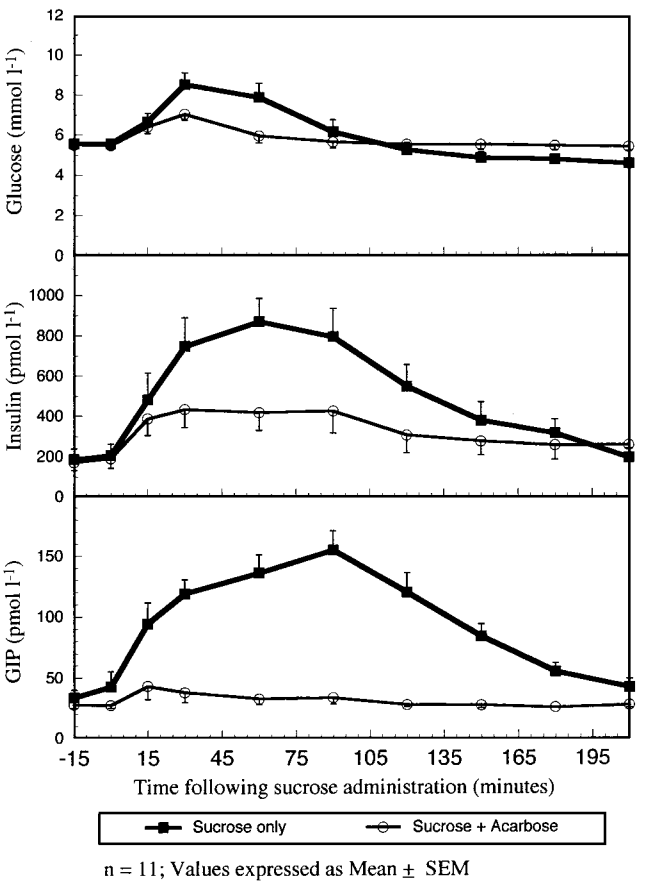

Figure 1. Plasma responses of Glucose, Insulin, and GIP to sucrose administration with and without acarbose

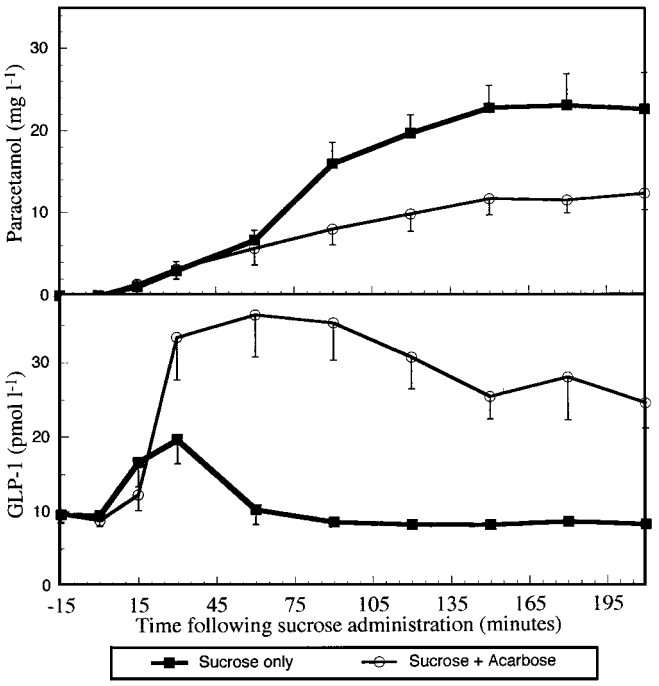

Figure 2. Plasma responses of Paracetamol and GLP-1 to sucrose administration with and without acarbose (n = 11; values expressed as Mean ± SEM)

lower after sucrose + acarbose than after sucrose alone ($p < 0.003$). However, there was no significant difference between the integrated plasma glucose responses to sucrose with and without acarbose.

Plasma insulin increased promptly in response to sucrose alone, peaking at 60 min and declining to baseline values by 210 min. The total and incremental integrated insulin reponses were significantly lower following sucrose + acarbose than after sucrose alone ($p < 0.0001$).

The prompt plasma GIP responses to sucrose was almost completely abolished by prior treatment with acarbose. There was a modest rise in plasma GLP-1 after sucrose alone, peaking at 30 min and returning to baseline at 60 min. When acarbose was given with sucrose, the GLP-1 response was enhanced, with higher values from 30 minutes onwards ($p < 0.02$), greater total and incremental responses ($p < 0.001$ and $p < 0.0001$, respectively) and only showed a modest decline by 210 min.

Following sucrose alone, plasma paracetamol levels rose steadily, reaching a plateau at 150 min. A similar response was seen following sucrose + acarbose but there was a divergence in the rate of rise from 60 min onwards, and the integrated paracetamol response was significantly lower following sucrose + acarbose than after sucrose alone ($p < 0.01$).

Discussion

Acarbose administration resulted in significantly reduced glucose, insulin, and GIP responses to ingestion sucrose. This is consistent with inhibition of brush border glucosidase.[5–7]

The markedly lower serum paracetamol profiles in the present study post-acarbose might be due to a slower rate of gastric emptying or reduced absorption of paracetamol from the upper small intestine. The presence of undigested and unabsorbed hyperosmolar sucrose solution in the small bowel results in osmotic fluid shifts and intestinal hurry[15] which might, in theory, reduce the contact time between the mucosa and paracetamol, and predispose to paracetamol malabsorption. However, paracetamol is a weakly acidic drug which exists in a largely unionized form in the small intestine and is therefore readily and rapidly absorbed at this site.[9,10] There is little evidence to indicate that acarbose impairs small intestinal absorption of either drugs or the products of digestion. Despite a single report indicating some inhibition of metformin absorption by acarbose,[16] other reports have shown that acarbose has no effect on the absorption of glucose[17] or of other drugs such as sulphonylurea, digoxin or propranolol[18,19] and the use of acarbose is not generally considered to pose problems

Table 1. Total (TAUC) and Incremental (IAUC) integrated responses for glucose, paracetamol, insulin,GIP, and GLP-1 following sucrose administration with and without acarbose

	Glucose (mM min^{-1})	Paracetamol (mg min^{-1})	Insulin (nM min^{-1})	GIP (nM min^{-1})	GLP-1 (pM min^{-1})
Sucrose load					
1. TAUC	1269	3048[a]	115.7[b]	21.5[c]	2172[b]
	(76)	(347)	(19.4)	(2.14)	(157)
2. IAUC	98.4		74.3[a]	13.4[c]	177[c]
	(50.1)		(11.5)	(1.9)	(152)
Acarbose + sucrose					
1. TAUC	1217	1650	71.2	6.54	6017
	(50)	(167)	(16.3)	(0.76)	(803)
2. IAUC	65.2		33.1	0.73	4080
	(23.4)		(8.9)	(0.41)	(750)

All results expressed as mean (SEM).
Sucrose significantly different from acarbose + sucrose; [a]$p < 0.01$; [b]$p < 0.001$; [c]$p < 0.0001$.

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in diabetic patients treated with acarbose and requiring other drug therapy. We therefore believe that osmotic malabsorption is unlikely to explain the whole delay in paracetamol responses post-acarbose, although this clearly requires confirmation using a more direct measure of gastric emptying.

Acute hyperglycaemia decreases the rate of gastric emptying.[20,21] The degree of hyperglycaemia is however unlikely to be a significant factor in this study as the circulating glucose levels were lower following the administration of acarbose.

The finding of a markedly exaggerated plasma GLP-1 response to sucrose when given with acarbose confirms previous studies.[22] Since both endogenous GLP-1 secretion and exogenous administration have been convincingly shown to delay gastric emptying,[23,24] it seems probable that this exaggerated response may be responsible for the delay in gastric emptying. The temporal relationship between the sustained rise in GLP-1 and the lower paracetamol levels up to 210 min after sucrose + acarbose supports this suggestion.

The mechanism for the sustained elevation of GLP-1 is unclear. Unlike GIP, the secretion of which is dependent upon active transport of nutrients across the enterocyte, GLP-1 secretion is stimulated by the presence of nutrients in the intestinal lumen. Thus, although treatment with acarbose may result in a more rapid intestinal transit time, the continued presence and osmotic effect of sucrose in the lumen may result in both enhanced and prolonged secretion of GLP-1. Since the increase in GLP-1 secretion occurs in the early postprandial period (peaking by 60 min), this may result in a self-reinforcing cycle whereby impaired digestion and absorption of sucrose enhances GLP-1 release; this delays complete gastric emptying, allowing slower release of sucrose into the duodenum and ileum, which, if incompletely digested and absorbed, would result in sustained secretion of GLP-1.

GIP was initially recognized for its inhibitory effects on the stomach[25] but it now seems unlikely that this is a physiologically important role.[26] The suppression of GIP secretion observed in this study is consistent with the inhibitory effect of acarbose on sucrose digestion and subsequent glucose absorption, and indicates that GIP is not involved in what appears to be a delay in gastric emptying.

One of the objectives in the treatment of diabetes is the avoidance of large postprandial excursions in plasma glucose. A number of strategies have been designed to achieve this, the most important of which are a reduction in the dietary intake of refined carbohydrate and an increase in the proportion of dietary carbohydrate in the unrefined form. By reducing the digestion and absorption of refined carbohydrate (especially sucrose), acarbose is a useful adjunctive therapy. The results of this study suggest that, in addition to its effect on digestive enzymes, acarbose may also contribute to a reduction in postprandial hyperglycaemia by delaying gastric emptying and thus reducing the release of nutrients from the stomach into the small intestine. In view of the fact that this is probably an indirect effect mediated by changes in gastrointestinal hormones but ultimately dependent on the known effect of acarbose on the digestion of carbohydrate, it is likely that the effect will be most marked in patients with poor dietary compliance. The delay in gasric emptying as well as the malabsorption of carbohydrates due to glucosidase inhibition may both have a mutually additive effect to produce the overall anti-hyperglycaemic effect of acarbose.

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